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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,936	HAMMOND ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-156* is/are pending in the application.

4a) Of the above claim(s) *37-39,46-51,101-103,110-115 and 121-156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36,40-45,52-100,104-109 and 116-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction requirement received on 1/3/05 has been entered. Claims 1-156 are pending in the instant application. Applicant's election with traverse of the subject matter of group I, claims 1-36, 40-45, 52-100, 104-109 and 116-120 is acknowledged. Claims 37-39, 46-51, 101-103, 110-115, and 121-156 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/3/05. Claims 1-36, 40-45, 52-100, 104-109 and 116-120 are currently under examination. An action on the merits follows.

Election/Restrictions

As noted above, the applicants have elected with traverse the subject matter of group I. The traversal is on the ground(s) that it would not be unduly burdensome on the examiner to search the claims of groups I-VII together. This is not found persuasive. The previous office action clearly set forth specific reasons why each of groups I-VII are separately patentable and why the search of these groups together would be unduly burdensome to the examiner, see pages 4-5 of the restriction requirement mailed on 7/1/04. The applicant has not set forth any specific arguments to the examiner's reasons for restriction. Therefore, the traversal is not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 or 365(c) as follows. It is noted that this application was granted filing status under Rule 1.47 and accorded a filing date of 5/3/01, see the Petition Decision mailed to applicants on 7/1/02 from the Office of Petitions. This applicant claims benefit or priority to 5 different series of parent applications, see page 1 of the instant specification, and the bibliographic data sheet attached to this action. The claims for priority to each series of applications are addressed separately below.

1) The applicant states that the instant application is a CIP of 09/609,080 filed on 6/30/00 and abandoned on 5/7/01. Although this application was incomplete, a retention fee was filed. As this application was co-pending with the instant application and meets the other requirements of 37 CFR 1.78, benefit of priority to parent application 09/609,080 is acknowledged.

However, no further benefit of priority to any of the older parent applications listed in this series is granted. Specifically, the applicant states that 09/609,080 is a CIP of 09/435,156. However, this application was abandoned on 2/2/00, and thus was not copending with the 09/609,080 application filed on 6/30/00. Thus, this application is not granted priority to parent application 09/435,156 for lack of co-pendency. Since priority has not been granted to the 09/435,156 application, further claims in this series to older applications cannot be granted. Thus, within this series of priority, the instant application is granted benefit of priority under 35 U.S.C. 120 to the 09/609,080 application with a filing date of 6/30/00.

2) This application claims priority as a CIP to PCT/US00/303045 filed on 11/3/00. Priority to this application is acknowledged.

3) This application claims priority as a CIP to PCT/US99/02702, filed on 2/09/99. This PCT application was published on 8/19/99 and the 30 month date for this international application expired on 8/1/00. Note that the 30 months are calculated from the priority date of the international application which in this instance was 2/11/98, the filing date of the 09/021,773 application. As such, the instant application was not co-pending with international application PCT/US99/02702. Therefore, priority to this application is denied. Since priority has not been granted to the PCT/US99/02702 international application, further claims in this series to older applications cannot be granted.

4) This application claims priority as a CIP to 09/068,102, filed on 4/30/98. This application was abandoned on 10/18/00 and thus was not co-pending with the instant application. As such, priority to this application is denied. Since priority has not been granted to the 09/068,102 application, further claims in this series to older applications cannot be granted.

5) This application claims priority as a CIP to 09/132,167, filed on 8/10/99, which issued as U.S. Patent No. 6,174,871 on 1/16/01. Since this application issued as a patent prior to the filing date of this application, it was not co-pending and thus benefit of priority is denied.

Therefore, based on the chains of priority set forth by the applicants and in view of the analysis of the claims for priority set forth above, the earliest effective filing date for the instant application has been determined to be that of parent application 09/609,080 which was filed on 6/30/00.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-24, 27, 40-45, 52-62, 65-88, 91, 104-109, and 116-120 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-110 of U.S. Patent No. 6,100,242 (8/8/00), hereafter referred to as the '242 patent. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-110 of the '242 patent represent a species of the instant claims. They are identical to the instant claims except that they are more narrowly limited to the species of vector which is a replication-deficient adenovirus, and to the species of sites of introduction which is the lumen of a coronary artery supplying blood to the myocardium (compare independent claims 1, 30, 58, and 86 in the '242 patent with instant claims 1 and 57). Further specific limitations to the independent claims present in instant claims 2-24, 27, 40-45, 52-56, 58-62, 65-88, 91, 104-109, and 116-120, are all recited in claims 2-29, 31-57, 59-85, and 87-110 of the '242 patent.

It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Therefore, the claims of the '242 patent, as a species of the instant broad claims, render the instant claims obvious.

Claims 1-24, 27, 40-45, 52-62, 65-88, 91, 104-109, and 116-120 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,174,871 (1/16/01), hereafter referred to as the '871 patent. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-21 of the '871 patent represent a species of the instant claims. Independent claims 1 and 20 of the '871 patent are identical to the instant claims 1 and 57 except that they are more narrowly limited to the species of vector which is a replication-deficient adenovirus, and to the species of sites and modes of introduction which is the direct intracoronary injection into the lumen of one or more coronary arteries. Further specific limitations to the independent claims present in instant claims 4-5, 8, 10-24, 27, 40-45, 52-56, 59-62, 65-66, 68-69, 72, 74-88, 91, 104-109, and 116-120, are all recited in claims 2-19 and 21.

It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Therefore, the claims of the '871 patent, as a species of the instant broad claims, render the instant claims obvious.

In regards to the recitation of the use of catheters to deliver the vectors in instant claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73, it is noted that the claims of the '871 patent are broader in that they simply recite intracoronary injection directly into the lumen of one or more coronary

arteries. However, the specification of the '871 patent clearly teaches that a preferred method of intracoronary injection involves the use of a catheter introduced at least about 1cm into the lumen of one or both coronary arteries or one or more saphenous veins ('871 patent, columns 4, 8, 11, and 15). Thus, it is clear from the teachings of the '871 specification that the limitations of claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73 not specifically recited in the claims are clearly encompassed by the '871 methods. As such, the methods recited in claims 1-18, and 25-41 of the '871 patent further render obvious instant claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73.

Claims 1-24, 27, 40-45, 52-62, 65-88, 91, 104-109, and 116-120 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18, and 25-41 of U.S. Patent No. 5,792,453 (8/11/98), hereafter referred to as the '453 patent. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-18, and 25-41 of the '453 patent represent a species of the instant claims. Independent claims 1 and 25 of the '453 patent are identical to the instant claims 1 and 57 except that they are more narrowly limited to the species of vector which is a replication-deficient adenovirus, and to the species of sites and modes of introduction which is the direct intracoronary injection into the lumen of one or more coronary arteries. Further specific limitations to the independent claims present in instant claims 4-5, 8, 10-24, 27, 40-45, 52-56, 59-62, 65-66, 68-69, 72, 74-88, 91, 104-109, and 116-120, are all recited in claims 2-18 and 26-41.

It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Therefore, the claims of the '453 patent, as a species of the instant broad claims, render the instant claims 1, 4-5, 8, 10-24, 27, 40-45, 52-57, 59-62, 65-66, 68-69, 72, 74-88, 91, 104-109, and 116-120 obvious.

In regards to the recitation of the use of catheters to deliver the vectors in instant claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73, it is noted that the claims of the '453 patent are broader in that they simply recite intracoronary injection directly into the lumen of one or more coronary arteries. However, the specification of the '453 patent clearly teaches that a preferred method of intracoronary injection involves the use of a catheter introduced at least about 1cm into the lumen of one or both coronary arteries or one or more saphenous veins ('453 patent, columns 4, 8, 11, and 15). Thus, it is clear from the teachings of the '453 specification that the limitations of claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73 not specifically recited in the claims are clearly encompassed by the '453 methods. As such, the methods recited in claims 1-18, and 25-41 of the '453 patent further render obvious instant claims 2-3, 6-7, 9, 57-58, 67, 70-71, and 73.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-24, 27, 40-45, 52-62, 65-88, 91, 104-109, and 116-120 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,792,453 (8/11/98), hereafter referred to as the '453 patent. The applicant broadly claims methods for increasing contractile function in the heart comprising delivering a transgene encoding an angiogenic protein or peptide to the myocardium of a patient by introducing the vector into at least one coronary artery (claim 1) and methods for increasing blood flow in an ischemic tissue of a patient comprising delivering a vector encoding an angiogenic protein to an ischemic region of the tissue (claim 57). The applicant further claims numerous additional limitations to these methods, most specifically wherein the vector is a replication-deficient adenovirus vector, wherein the vector is delivered from a catheter, wherein the transgene is linked to a CMV or cardiomyocyte-specific myosin heavy chain promoter, wherein the angiogenic protein is FGF or VEGF, wherein the vector predominantly transfects cardiac myocytes, and wherein the patient suffers from atherosclerosis or myocardial ischemia.

The '453 patent teaches methods of stimulating coronary collateral vessel development and methods of treating myocardial ischemia comprising the direct intracoronary injection of replication-deficient adenovirus encoding an angiogenic protein or peptide into one or both coronary arteries ('453 patent, claims 1-18, and 25-41). The '453 patent further teaches that the intracoronary injection involves the use of a catheter introduced at least about 1cm into the lumen of one or both coronary arteries or one or more saphenous veins ('453 patent, columns 4, 8, 11, and 15). The '453 patent further teaches that following these methods results in increased contractile function and heart thickening ('453 patent, column 15). Further specific limitations to dosages, specific proteins, and specific promoters recited in instant claims 2-24, 27, 40-45, 52-56, 58-62, 65-88, 91, 104-109, and 116-120, can be found in claims 2-18, and 26-41 of the '453 patent. Thus, by teaching all the limitations of the claims as written, the '453 patent anticipates the instant claims.

Claims 57, 60, 63-66, 74-80, 84-91, 93-100, 104, 109, and 116-120 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,121,246 (9/19/00), hereafter referred to as Isner. The claims recite methods for increasing blood flow in an ischemic tissue of a patient comprising delivering a vector encoding an angiogenic protein to an ischemic region of the tissue (claim 57). The claims further recite said methods wherein the vector is delivered to skeletal muscle, wherein the vector is a replication-deficient adenovirus, and wherein the more than one angiogenic protein is delivered, specifically FGF and VEGF or IGF.

Isner teaches methods of increasing blood flow in ischemic tissue by direct injection of DNA encoding an angiogenic protein operatively linked to a secretory signal sequence and a

promoter into ischemic muscle tissue, wherein the angiogenic protein is VEGF, acidic or basic FGF, IGF, or PDGF (Isner , claim 1 and 16). Isner further teaches said methods wherein the host has myocardial ischemia, limb ischemia, and ischemic cardiomyopathy (Isner, column 2, and abstract). Isner also teaches that the DNA encoding the angiogenic protein can be part of a recombinant replication-deficient adenovirus, and that the promoter can be CMV (Isner, column 5, and claims 15 or 30). In addition, Isner teaches that nucleic acid encoding two or more different angiogenic proteins can be delivered to optimize therapeutic outcome (Isner et al., column 6, lines 4-9). In particular, Isner teaches the combination of VEGF and bFGF, however any combination of 2 of more of the angiogenic factors specifically taught by Isner are clearly encompassed by these teachings including bFGF and IGF or VEGF, bFGF, and IGF (Isner, column 6, lines 6-9, and claim 1). In regards to specific therapeutic effects recited in the claims, i.e. increase in contractile function or stimulation of collateral vessel development, it is noted that as Isner clearly teaches the delivery of DNA encoding angiogenic proteins to ischemic muscle tissue, any therapeutic effects derived from its expression are inherent to the Isner method. The MPEP states that "when the claim recites using an old composition or structure and the 'use' is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F. 2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)". MPEP 2112.02. Thus, by teachings all the limitations of the claims as written, Isner anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-26 and 29-36 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,792,453 (8/11/98), hereafter referred to as the '453 patent, in view of US Patent No. 6,121,246 (9/19/00), hereafter referred to as Isner. The applicant claims methods for increasing contractile function in the heart comprising delivering a transgene encoding an angiogenic protein or peptide to the myocardium of a patient by introducing the vector into at least one coronary artery, wherein the angiogenic protein is IGF, or wherein the vector further comprises more than one angiogenic protein, such as VEGF and FGF, or VEGF and IGF, or VEGF and IGF and FGF.

The '453 patent teaches methods of stimulating coronary collateral vessel development and methods of treating myocardial ischemia comprising the direct intracoronary injection of

replication-deficient adenovirus encoding an angiogenic protein or peptide into one or both coronary arteries ('453 patent, claims 1-18, and 25-41). While the '453 broadly recites the use of any angiogenic protein, it only specifically provides VEGF and the FGF family as examples. Isner supplements the '453 patent by teaching similar methods of stimulating vessel growth in ischemia muscle tissue by administering replication-deficient adenovirus encoding an angiogenic protein selected from a group including VEGF, FGF, and IGF (Isner, claims 1 and 16). Thus, based on motivation provided by the '453 patent to use any angiogenic protein, and the specific teachings of Isner to use nucleic acid encoding IGF to treat ischemic muscle tissue and myocardial ischemia in particular, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the nucleic acid encoding IGF in the methods for increasing contractile function in the heart taught by the '453 patent with a reasonable expectation of success.

The '453 patent also does not specifically teach that the adenovirus encodes more than one angiogenic protein. Isner further supplements the '453 patent by teaching that nucleic acid encoding two or more different angiogenic proteins can be delivered to optimize therapeutic outcome in treating ischemic disease (Isner et al., column 6, lines 4-9). In particular, Isner teaches the combination of VEGF and bFGF, however any combination of 2 of more of the angiogenic factors specifically taught by Isner are clearly encompassed by these teachings including bFGF and IGF or VEGF, bFGF, and IGF (Isner, column 6, lines 6-9, and claim 1). Based on the motivation to administer a vector such as an adenoviral vector encoding more than one angiogenic protein in order to optimize therapeutic outcome in the treatment of ischemia as taught by Isner, it would have been *prima facie* obvious to the skilled artisan to modify the

replication-deficient adenovirus encoding an angiogenic protein as taught by the '453 patent to encode a second angiogenic protein. Based on the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in making such a recombinant adenovirus and in using the vector to induce vessel growth in ischemic muscle tissue.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36, 40-45, 52-100, 104-109 and 116-120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing contractile function in the heart, and methods for increasing blood flow in an ischemic heart tissue, comprising direct intracoronary administration of a replication deficient adenovirus encoding FGF into the lumen or one or both coronary arteries, does not reasonably provide enablement for said methods using any vector encoding any angiogenic protein or combination of proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for the use of any and all vectors which encode one or more angiogenic proteins for in vivo transfection or transduction of vascular and/or ischemic tissue wherein a therapeutic effect on a cardiovascular disease or

ischemic disease is observed. The specification discloses that any DNA or RNA based vector such as plasmid, adenoviral, retroviral, adeno-associated viral, and poxvirus vectors can be used to express therapeutic levels of one or more angiogenic proteins in the instant methods. The specification's working examples, however, are limited to the use of replication deficient adenoviral constructs. The specification does not provide sufficient guidance concerning the parameters affecting in vivo delivery of vectors other than replication incompetent adenoviral vectors, such as the level of transfection of vascular cells and the level of expression of therapeutic proteins required *in vivo* to generate collateral vessel development or to ameliorate any symptom of cardiovascular disease. At the time of filing, the art teaches the unpredictability of achieving therapeutic levels of gene expression using currently available *in vivo* expression systems. For example, Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2).Verma further points out that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector - " .. [T]he search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and

page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2). Thus, the art at the time of filing establishes the unpredictability in targeting and expressing therapeutic levels of nucleic acids of interest in particular cells *in vivo*. The specification does not provide sufficient guidance to overcome this high degree of art recognized unpredictability for using vectors other than replication deficient adenoviral vectors.

The specification further does not provide sufficient guidance for the therapeutic expression of any angiogenic protein(s) to treat any and all cardiovascular or ischemic diseases. The specification broadly discloses a long list of potential angiogenic factors including VEGF, FGF, IGF, PDGF, hypoxia-inducible factor, and angiogenic polypeptide regulators for use in the instant methods. However, the working examples provided are limited to the therapeutic expression of FGF-2, FGF-4, and FGF-5 using replication deficient adenovirus delivery directly into the coronary arteries using a catheter. The examples demonstrate that all three FGF family members, when expressed using this particular methodology, are capable of increasing contractile function and perfusion of the heart. However, the specification has not provided any evidence that any of the other angiogenic proteins disclosed, either alone or in combination, are capable of similar effects, or that there is an art recognized nexus between the functional

activities of FGF family members and other functionally different proteins such as IGF, PDGF, hypoxia inducible factor, or an angiogenic polypeptide regulator. There are many cardiovascular diseases which lead to impaired blood supply to the heart or other organs including hypertension, atherosclerosis, and restenosis. Vascular endothelial cell dysfunction is common to many cardiovascular diseases, particularly those aforementioned. Treatment of atherosclerosis, restenosis, or primary hypertension with a vascular endothelial cell activator like VEGF may lead to exacerbation of the disease rather than amelioration regardless of increased angiogenesis. For instance, Lazarous et al. teaches that treatment of dogs suffering from mechanically induced cardiac ischemia and iliofemoral balloon catheter denudation injury with VEGF resulted in an unexpected increase in stenosis at the site of balloon injury (Lazarous et al. (1996) Circulation, Vol. 94, page 1080, column 2, paragraph 1, and page 1081, column 1, paragraphs 2-3). It is further noted that the specification's working examples utilize a pig model of induced cardiac ischemia by ameroid closure of the proximal left circumflex artery. While this model reproduces generalized ischemia in the blocked region, it does not accurately reflect the conditions present in arteries blocked by atherosclerotic lesions or restenosis which include vascular endothelial cell dysfunction and smooth muscle cell dysplasia.

Thus, based on the art recognized unpredictability for in vivo delivery and expression of vectors encoding therapeutic proteins for the treatment of disease at the time of filing, the lack of guidance provided by the specification for the parameters associated with the delivery and expression of therapeutic genes in vivo using expression vectors other than replication deficient adenoviral vectors, the complexity and diversity of ischemic conditions, the limitation of the workings examples to the administration of replication deficient adenoviral vectors encoding

FGF family members, the unpredictability that other "angiogenic" proteins encompassed by the claims would function similarly to FGF, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the scope of the invention as claimed at the time of filing.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

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